

Method <sup>of</sup> ~~treating~~ a bactericidal infection  
~~Novel Method of Treatment~~

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 20  
 This application is a CIP of 09/644,819 filed 4/6/2000, which claims benefit of 60/129,074 filed 4/13/1999 and claims benefit of 06/150,729 filed 8/15/1999 and claims benefit of 60/159,813 filed 10/15/1999.

Field of the Invention

5 This invention relates to a novel method of treatment using amoxicillin and potassium clavulanate and for novel formulations, in particular tablet formulations, for use in such methods.

Background of the Invention

10 Amoxicillin and potassium clavulanate are respectively a known  $\beta$ -lactam antibiotic and a known  $\beta$ -lactamase inhibitor. Products comprising amoxicillin and potassium clavulanate are marketed under the trade name "Augmentin" by SmithKline Beecham. Such products are particularly effective for treatment of community acquired infections, in particular upper respiratory tract infections in adults and otitis media in  
 15 children.

Various tablet formulations of amoxicillin and potassium clavulanate have been approved for marketing, comprising various different weights and ratios of amoxicillin and potassium clavulanate, for instance, conventional swallow tablets comprising  
 20 250/125, 500/125, 500/62.5, and 875/125 mg amoxicillin/clavulanic acid (in the form of potassium clavulanate). Such tablets comprise amoxicillin and clavulanic acid in the ratio 2:1, 4:1, 8:1 and 7:1, respectively. The 875/125 mg tablet was developed to provide a tablet formulation which could be administered in a bid (twice daily) dosage regimen. It is also marketed for tid (three times daily) dosing, in Italy and Spain. The  
 25 500/62.5 mg tablet was also developed to provide a tablet formulation which could be administered in a bid dosage regimen, two such tablets being taken every 12h, in preference to a single 1000/125 mg tablet. A 1000/125mg single dosage is also available, in France, but as a single dosage sachet rather than a tablet. Typically, the approved regimens provides a single dosage of 125 mg of potassium clavulanate.

In addition, WO 97/09042 (SmithKline Beecham) describes tablet formulations  
 30 comprising amoxicillin and clavulanic acid in a ratio in the range 12:1 to 20:1, preferably 14:1. Furthermore, it is suggested that the preferred dosage of 1750/125mg may be provided as two tablets, the first comprising 875/125mg amoxicillin and clavulanic acid and the second 875 mg amoxicillin. The 14:1 ratio is said to be useful for the empiric treatment of bacterial infection potentially caused by drug resistant *S pneumoniae* (DRSP). This patent application also describes paediatric formulations  
 35 comprising amoxicillin and clavulanate in a 14:1 ratio, for administering amoxicillin

dosages of 90 mg/kg/day. Data suggest that such a dosage may provide antibiotic concentrations sufficient to eradicate DRSP with amoxicillin +/- clavulanic acid MICs  $\leq$  4  $\mu$ g/ml (Bottenfield et al, Pediatr Infect Dis J, 1998, 17, 963-8).

WO 94/16696 (SmithKline Beecham) discloses generally that clavulanic acid  
5 may unexpectedly enhance the efficacy of amoxicillin against microorganisms having a resistant mechanism which is not  $\beta$ -lactamase mediated.

Existing marketed tablet formulations of amoxicillin and potassium clavulanate are conventional in that they provide immediate release of the active ingredients once the tablet reaches the stomach. There has also been some interest in developing  
10 formulations in which the release profile is modified, to allow for a longer interval between dosages, for instances, every 12 hours (bid, q12h), rather than every 8 hours (tid, q8h).

Thus, for instance, WO 95/20946 (SmithKline Beecham) describes layered tablets comprising amoxicillin and, optionally, potassium clavulanate, having a first  
15 layer which is an immediate release layer and a second layer which is a slow release layer. The broadest ratio of amoxicillin to clavulanic acid is 30:1 to 1:1, with a preferred range of 8:1 to 1:1. Amoxicillin is suitably in the form of amoxicillin trihydrate. Examples provided of such bilayered tablets have amoxicillin trihydrate in the immediate release layer and amoxicillin plus clavulanate in the slow release layer.  
20 Multi-layered tablets are described more generically in WO 94/06416 (Jagotec AG). Further bilayered tablets comprising clavulanic acid and amoxicillin are described in WO 98/05305 (Quadrant Holdings Ltd). In such tablets, a first layer comprises amoxicillin and a second layer comprises clavulanate and the excipient trehalose, to stabilise the clavulanate component.

25 In addition, WO 95/28148 (SmithKline Beecham) describes amoxicillin/potassium clavulanate tablet formulations having a core containing amoxicillin and potassium clavulanate coated with a release retarding agent and surrounded by an outer casing layer of amoxicillin and potassium clavulanate. The release retarding agent is an enteric coating, so that there is an immediate release of the  
30 contents of the outer core, followed by a second phase from the core which is delayed until the core reaches the intestine. Furthermore, WO 96/04908 (SmithKline Beecham) describes amoxicillin/potassium clavulanate tablet formulations which comprise amoxicillin and potassium clavulanate in a matrix, for immediate release, and granules in a delayed release form comprising amoxicillin and potassium clavulanate. Such  
35 granules are coated with an enteric coating, so release is delayed until the granules reach the intestine. WO 96/04908 (SmithKline Beecham) describes amoxicillin/potassium

clavulanate delayed or sustained release formulations formed from granules which have a core comprising amoxicillin and potassium clavulanate, surrounded by a layer comprising amoxicillin. WO 94/27557 (SmithKline Beecham) describes controlled release formulations of amoxicillin and clavulanic acid prepared using a hydrophobic waxy material which is then subjected to thermal infusion.

Controlled release formulations comprising amoxicillin have been described by several groups. Thus, Arancibia *et al* ((Int J of Clin Pharm, Ther and Tox, 1987, 25, 97-100) describe the pharmacokinetic properties and bioavailability of a controlled release formulation comprising 500 mg of amoxicillin. No further details of the formulation are provided. The formulation was however designed to release 21 to 35% during the first 60 minutes, 51 to 66% at 4 hours, 70 to 80% at 6 hours, 81 to 90% at 8 hours and more than 94% at 12 hours. They however found little, if any, correlation between the *in vitro* dissolution rate and the pharmacokinetic behaviour in the body. Hilton *et al* (International Journal of Pharmaceutics, 1992, 86, 79-88) described an alternative controlled release tablet having a hydrophilic polymer matrix and a gas release system, to provide intragastric buoyancy, to enhance gastric retention time. This showed no advantage over a conventional capsule formulation, with bioavailability being diminished. In contrast, Hilton *et al* (Journal of Pharmaceutical Sciences, 1993, 82, 737-743) described a 750 mg controlled release tablet incorporating the enteric polymer hydroxypropylmethyl cellulose acetate succinate. This however failed to show any advantage over a conventional capsule. In particular, the bioavailability was reduced to 64.6% compared with the same dosage provided in a capsule. More recently, Hoffman *et al* (Journal of Controlled Release, 1998, 54, 29-37 and WO 98/22091) have described a tablet comprising 500 mg of amoxicillin in a matrix comprising hydroxypropyl methyl cellulose, designed to release 50% of its contents in the first three hours and complete the drug release process over eight hours. The time above MIC was found to be significantly extended, compared to a capsule formulation, but not enough for a 12 h dosing interval. The discussion is in the context of a theoretical MIC of 0.2 µg/ml.

It has therefore, been determined that there is a continuing need to provide new dosage regimens for amoxicillin/clavulanate which are effective against more resistant bacteria.

#### Summary of the Invention

The present invention relates to a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxicillin and potassium clavulanate such that the amount of amoxicillin is in the

range 1900 to 2600 mg and the amount of potassium clavulanate is such that the weight ratio of amoxicillin to clavulanate is from about 2:1 to 20:1, and at a dosage regiment/interval of about 12 hours. Suitably, the infection is caused by the organisms *S pneumoniae* (including Drug Resistant and Penicillin Resistant *S pneumoniae*), *H influenzae* and/or *M catarrhalis*.

The present invention also relates to a modified release pharmaceutical formulation comprising amoxicillin and potassium clavulanate in the ratio from 2:1 to 20:1 in which all of the potassium clavulanate and a first part of amoxicillin are formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and the first part of amoxicillin, to form an immediate release phase, and further comprising a second part of amoxicillin formulated with pharmaceutically acceptable excipients which allow for slow release of the second part of amoxicillin, to form a slow release phase.

The present invention also relates to an immediate release pharmaceutical tablet formulation comprising 1000 mg  $\pm 5\%$  amoxicillin and 62.5 mg  $\pm 5\%$  potassium clavulanate, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers.

The present invention also relates to an immediate release pharmaceutical formulation in the form of a single dose sachet comprising 2000, 2250 or 2500 mg  $\pm 5\%$  amoxicillin and 125 mg  $\pm 5\%$  potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with pharmaceutically acceptable excipients or carriers.

Other suitable modified or immediate release formulations are described herein in greater detail.

#### Brief Description of the Drawings

Figure 1 shows the structure of various types of layered tablets of the present invention, in particular the structure of substantially cylindrical compressed tablets are shown in longitudinal section. In

Fig 1A, shows a tablet comprising a first layer (1) and a second layer (2), without any barrier layer or coating layer.

Fig 1B, shows a tablet comprising a first layer (1), a second layer (2), and a barrier layer (3) sandwiched between the first and second layers (1) and (2).

Fig 1C, shows a tablet comprising a first layer (1), a second layer (2), and a barrier layer (3) located on the end face of the second layer (2).

Fig 1D, shows a tablet comprising a first layer (1), a second layer (2), a barrier layer (3) sandwiched between the first and second layers (1) and (2), and a coating layer (4) which partly covers the tablet. The dotted line shows the possibility of the coating layer (4A) covering the entire tablet.

5 Fig. 1E, shows a tablet comprising a first layer (1) a second layer (2), and a third layer (3) intermediate between the first and second layers (1) and (2). All three of these layers (1), (2) and (3) include active material content.

Figure 2 demonstrates modified release tablets prepared according to the process flow diagram shown in Figure 2. In brief, immediate and modified release blends are prepared which involve initial sieving and milling, as indicated, before roller compaction in a Chilsonater and further milling, sieving and blending.

Figure 3 demonstrates the dissolution profile for tablets of Examples 1 and 2.

Figure 4 demonstrate the pharmacokinetic profiles of Study A

15 Figure 5 demonstrates the pharmacokinetic profile for amoxicillin plasma concentration for Study B (in which A is formulation V, B is formulation VI, D is formulation VIII).

#### Detailed Description of the Invention

20 Part of the challenge in providing formulations of amoxicillin in which the drug release is effectively modified (and a ready explanation for the lack of success in the studies already referenced) is the relatively narrow window for absorption of the drug in the small intestine and the relatively short half life of the drug. Furthermore, the rapid elimination of amoxicillin (excretion half-life is 1.3 hours) makes it difficult to maintain serum levels as clearance from the body is very rapid.

25 In existing tablet formulations comprising amoxicillin and potassium clavulanate, amoxicillin is present in the form amoxicillin trihydrate, as the use of this form provides tablets with greater storage stability than those in which amoxicillin is present as sodium amoxicillin (see GB 2 005 538, Beecham Group Ltd). Sodium amoxicillin is however used as the amoxicillin component in existing formulations of  
30 amoxicillin and potassium clavulanate adapted for IV administration. The form of sodium amoxicillin used is a spray-dried form. In addition, EP 0 131 147-A1 (Beecham Group plc) describes a further form of sodium amoxicillin, so-called "crystalline sodium amoxicillin". A further process for preparing salts of amoxicillin, including sodium amoxicillin, is described in WO 99/62910 (SmithKline Beecham). Sodium amoxicillin  
35 is relatively water soluble in comparison to amoxicillin trihydrate.

Formulations comprising clavulanic acid and a pharmaceutically acceptable organic acid or a salt-like derivative thereof, for example calcium citrate, have been

described in WO 96/07408 (SmithKline Beecham). In such formulations, it is postulated that the presence of the calcium citrate would help suppress the gastro-intestinal intolerance associated with oral dosing of clavulanate-containing products.

Furthermore, US patent No. 5 051 262 (Elan Corp) describes the incorporation of an organic acid into a modified release formulation, to provide a microenvironment in which the locally modified pH helps to protect the active ingredient from degradation.

Of concern is the increasing resistance of pathogenic organisms, such as those found in respiratory tract infections, to anti-infective agents such as amoxicillin/potassium clavulanate, in particular drug resistant *S pneumoniae*. Increased resistance to penicillin of *S pneumoniae* (due to modified penicillin binding proteins) is developing around the world and is affecting clinical outcomes (see for instance Applebaum P C, Ped Inf Dis J, 1996, 15(10), 932-9). These penicillin resistant *S pneumoniae* (PRSP) have also been termed "DRSP" as they often exhibit decreased susceptibility not only to penicillin but also to a wider range of antimicrobial classes, including macrolides, azalides, beta-lactams, sulfonamides and tetracyclines. Amoxicillin (with or without clavulanate), along with some of the newer quinolones, has remained among the most active oral drugs against the increasingly resistant isolates of *S pneumoniae*, based on both MIC levels and pharmacokinetic properties of these compounds. Resistance rates (and MICs) have however continued to increase. Penicillin resistance in *S. pneumoniae* can be assessed according to criteria developed by the National Committee for Clinical Laboratory Standards (NCCLS), as follows: susceptible strains have MICs of  $\leq 0.06$   $\mu\text{g/ml}$ , intermediate resistance is defined as an MIC in the range 0.12 to 1.0  $\mu\text{g/ml}$  whilst penicillin resistance is defined as an MIC of  $\geq 2$   $\mu\text{g/ml}$ . Furthermore, it is found that some 10% of pneumococci now have an amoxicillin MIC of 2  $\mu\text{g/ml}$ .

There is consequently a need to provide new formulations of amoxicillin/clavulanate that combine the known safety profile and broad spectrum with improved activity against DRSP, including PRSP, with higher MICs in empiric treatment of respiratory infections where *S pneumoniae*, *H influenzae* and *M catarrhalis* are likely pathogens.

For  $\beta$ -lactams, including amoxicillin, it is recognised that the time above minimum inhibitory concentration ( $T > \text{MIC}$ ) is the pharmacodynamic parameter most closely related to efficacy. For a variety of  $\beta$ -lactams, a bacteriological cure rate of 85 to 100% is achieved when serum concentrations exceed the MIC for more than about 40% of the dosing interval (Craig and Andes, Ped Inf Dis J, 1996, 15, 255-259). For a 12 hour dosing interval, this is about 4.8 hours.

A further parameter which may be of importance is the ratio of the maximum plasma concentration ( $C_{max}$ ) to the MIC value, as this may be related to the potential to select for resistance. Too low a ratio may encourage the development of resistant strains. Preferably, the plasma  $C_{max}$  value is well above the MIC value, for instance, at least two times, more preferably at least three times, most preferably at least four times, the MIC value.

In a clinical study using the existing Augmentin 875/125mg tablet, it was found that, when dosed at 12 hour intervals, the time above MIC was about 40% for an MIC of 2  $\mu\text{g/ml}$  but only about 30% for an MIC of 4  $\mu\text{g/ml}$ . The existing Augmentin 875/125mg tablet has a  $C_{max}$  value of  $11.6 \pm 2.8 \mu\text{g/ml}$  (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802).

Based on the foregoing considerations, there is a continuing need to provide new dosage regimens for amoxicillin/clavulanate giving optimised pharmacokinetic profiles for amoxicillin whilst not compromising the bioavailability of clavulanate, so that therapy is maximised, particularly against more resistant bacteria whilst the (further) development of resistance is minimised. It has now been found that such can be achieved using higher dosages of amoxicillin than previously contemplated.

Accordingly, in a first aspect, the present invention provides for a method of treating bacterial infections in humans which comprises orally administering thereto a therapeutically effective amount of amoxicillin and potassium clavulanate such that the amount of amoxicillin is in the range 1900 to 2600 mg, preferably 1950 to 2550 mg, and the amount of potassium clavulanate is such that the weight ratio of amoxicillin to clavulanate is from 2:1 to 20:1, preferably 7:1 to 20:1, more preferably 14:1 to 20:1, at intervals of about 12 hours (hereinafter "h").

Preferably, the dosage regimen provides a mean plasma concentration of amoxicillin of 4  $\mu\text{g/mL}$  for at least 4.4 h, preferably at least 4.6 h, more preferably at least 4.8 h, most preferably for about 6 h or longer.

More preferably, the dosage regimen provides a mean plasma concentration of amoxicillin of 8  $\mu\text{g/ml}$  for at least 4.4 h, more preferably at least 4.6 h, most preferably at least 4.8 h.

Preferably, the dosage regimen provides a mean maximum plasma concentration ( $C_{max}$ ) of amoxicillin which is at least 8  $\mu\text{g/mL}$ , preferably at least 12  $\mu\text{g/mL}$ , yet more preferably at least 14  $\mu\text{g/mL}$ , most preferably at least 16  $\mu\text{g/mL}$ .

Preferably, the mean plasma concentration of amoxicillin and the mean maximum plasma concentration of amoxicillin are measured after oral administration of a formulation comprising amoxicillin at the start of a light meal.

In a further aspect, the present invention provides for a method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxicillin and potassium clavulanate such that the amount of amoxicillin is in the range 1400 to 1900 mg, preferably 1500 to 1900 mg, and the amount of potassium clavulanate is such that the weight ratio of amoxicillin to clavulanate is from 2:1 to 14:1, preferably 7:1 to 14:1, more preferably 12:1 to 14:1, at intervals of about 12 h, such that the dosage regimen provides a mean plasma concentration of amoxicillin of 4 µg/mL for at least 4.4 h, preferably at least 4.6 h, more preferably at least 4.8h, most preferably for about 6h or longer; more preferably, a mean plasma concentration of amoxicillin of 8 µg/ml for at least 4.4 h, more preferably at least 4.6 h, most preferably at least 4.8 h, and a mean maximum plasma concentration ( $C_{max}$ ) of amoxicillin which is at least 8 µg/mL, preferably at least 12 µg/mL, yet more preferably at least 14 µg/mL, most preferably at least 16 µg/mL.

Bacterial infections amenable to the present invention include infections caused by the organisms *S pneumoniae* (including Drug Resistant *S pneumoniae* (DRSP), for instance Penicillin Resistant *S pneumoniae* (PRSP)), and/or the β-lactamase producing respiratory pathogens, most notably *H influenzae* and *M catarrhalis*, such as respiratory tract infections, including community acquired pneumoniae (CAP), acute exacerbations of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS), where the higher break points achievable through the improved pharmacokinetic profile will be especially advantageous compared to existing antibacterial agents. Most outpatient respiratory infections are caused by either *S pneumoniae* and/or the β-lactamase producing bacteria and are treated empirically so there is a continuing need for a method of treatment, such as the present invention, that provides a spectrum of activity that covers all such pathogens. The duration of therapy will generally between 7 and 14 days, typically 7 days for indications such as acute exacerbations of chronic bronchitis but 10 days for acute bacterial sinusitis. Typically, the dosages regimens are designed for adult patients, rather than paediatric patients.

The term "amoxicillin" is used generically to refer to amoxicillin or an alkaline salt thereof, in particular amoxicillin trihydrate and (crystallised) sodium amoxicillin, without distinction and unless otherwise indicated.

Unless otherwise indicated, weights of amoxicillin and (potassium) clavulanate refer to the equivalent weights of the corresponding free acids. In addition, it will be appreciated that in practice, weights of amoxicillin and clavulanate to be incorporated into a formulation will be further adjusted, in accord with conventional practice, to take account of the potency of the amoxicillin and clavulanate.

In a first embodiment, a dosage of amoxicillin of from 1900 to 2600 mg and a corresponding amount of potassium clavulanate may delivered from an immediate release formulation. Accordingly, in a further aspect, the present invention provides for method of treating bacterial infections in humans which comprises administering thereto  
5 a therapeutically effective amount of amoxicillin and potassium clavulanate such that the amount of amoxicillin is in the range 1900 to 2600, preferably 1950 to 2550 mg, and the amount of potassium clavulanate is such that the weight ratio of amoxicillin to clavulanate is from 2:1 to 20:1, preferably 7:1 to 20:1, more preferably 14:1 to 20:1, at intervals of about 12 h, wherein the dosage is delivered from an immediate formulation.

10 As used herein, the term "immediate release" refers to the release of the majority of the active material content within a relatively short time, for example within 1 hour, preferably within 30 minutes, after oral ingestion. Examples of such immediate release formulations include conventional swallow tablets, dispersible tablets, chewable tablets, single dose sachets and capsules.

15 Representative dosages include 2000/125, 2250/125 and 2500/125 mg of amoxicillin and potassium clavulanate, respectively. A preferred dosage is 2000/125 mg of amoxicillin and potassium clavulanate.

The dosage in an immediate release formulation may be provided as a single tablet, for instance a dispersible tablet, a chewable tablet which may also be ,  
20 effervescent and/or dispersible, a single dose capsule or a single dosage sachet, comprising, for instance, 2000, 2250 or 2500 mg amoxicillin and 125 mg potassium clavulanate. Alternatively, the dosage may be made up of a number of smaller tablets or capsules, for instance, 2, 3 or 4, some of which may be the same and some of which may comprise amoxicillin only and no potassium clavulanate. Representative such smaller  
25 tablets include swallow tablets, dispersible tablets and chewable tablets which may also be effervescent and/or dispersible. Thus, for instance, a dosage of 2000 mg amoxicillin and 125 mg potassium clavulanate may be provided by a combination of three tablets each comprising 500 mg amoxicillin and one tablet comprising 500 mg amoxicillin and 125 mg potassium clavulanate. Alternatively, such a dosage may be provided by two  
30 tablets each comprising 1000/62.5 mg amoxicillin/potassium clavulanate. In addition, a dosage of 2250 mg amoxicillin and 125 mg potassium clavulanate may be provided by a combination of four tablets comprising 500 mg amoxicillin and one tablet comprising 250 mg amoxicillin and 125 mg potassium clavulanate or two tablets comprising 875 mg amoxicillin and one tablet comprising 500 mg amoxicillin and 125 mg potassium  
35 clavulanate. Furthermore, a dosage of 2500 mg amoxicillin and 125 mg potassium clavulanate may be provided by a combination of four tablet comprising 500 mg

amoxicillin and one tablet comprising 500 mg amoxicillin and 125 mg potassium clavulanate. Tablets comprising 500 and 875 mg amoxicillin and 250/125, 500/125 and 875/125 mg amoxicillin/potassium clavulanate are already commercially available.

It will be appreciated that immediate release tablets comprising 1000/62.5 mg are novel. Accordingly, in a further aspect, the present invention provides for an immediate release pharmaceutical tablet formulation comprising 1000 mg  $\pm 5\%$  amoxicillin and 62.5 mg  $\pm 5\%$  potassium clavulanate, in a nominal ratio of about 16:1, in combination with pharmaceutically acceptable excipients or carriers. Immediate release tablets comprising 1000/62.5 mg can be readily prepared by adapting compositions previously described for 875/125 and 1000/125 mg tablets (see for instance, WO 95/28927 and WO 98/35672, SmithKline Beecham).

It will also be appreciated that immediate release single dosage sachets comprising 2000/125 mg, 2250/125 mg or 2500/125 mg, or the corresponding half quantities thereof, are novel. Accordingly, in a further aspect, the present invention provides for an immediate release pharmaceutical formulation in the form of a single dose sachet comprising 2000, 2250 or 2500 mg  $\pm 5\%$  amoxicillin and 125 mg  $\pm 5\%$  potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with pharmaceutically acceptable excipients or carriers. Such sachets can be readily prepared by adapting compositions previously described for 875/125 and 1000/125 mg sachets (see for instance, WO 92/19277 and WO 98/35672, SmithKline Beecham).

It will be further appreciated that immediate release chewable tablets comprising 2000, 2250 or 2500/125 mg are novel. Accordingly, in a further aspect, the present invention provides for an immediate release pharmaceutical formulation in the form of a chewable, optionally effervescent, tablet comprising 2000, 2250, or 2500 mg amoxicillin and 125 mg  $\pm 5\%$  potassium clavulanate, in a nominal ratio of about 16:1, 18:1 or 20:1, respectively, or the corresponding half quantities thereof, in combination with a chewable base and, if effervescent, an effervescent couple, and other pharmaceutically acceptable excipients or carriers. Such chewable tablets can be readily prepared by adapting compositions previously described for chewable tablets comprising amoxicillin and potassium clavulanate (see for instance, EP-A-0 396 335, Beecham Group and WO 98/35672, SmithKline Beecham).

In a second embodiment, a dosage of amoxicillin of from 1900 to 2600 mg and a corresponding amount of potassium clavulanate may be delivered from a modified release formulation. Accordingly, in a further aspect, the present invention provides for method of treating bacterial infections in humans which comprises administering thereto

a therapeutically effective amount of amoxicillin and potassium clavulanate such that the amount of amoxicillin is in the range 1900 to 2600 mg, preferably 1950 to 2550 mg, and potassium clavulanate is present in a pro rata amount such that the weight ratio of amoxicillin to potassium clavulanate is from 2:1 to 20:1, preferably 7:1 to 20:1, more preferably 14:1 to 20:1, at intervals of about 12 h, in which the dosage is delivered from a modified release formulation.

In a third embodiment, a dosage of amoxicillin of from 1400 to 1900 mg and a corresponding amount of clavulanate may be delivered from the modified release formulation. Accordingly, in a further aspect, the present invention provides for method of treating bacterial infections in humans which comprises administering thereto a therapeutically effective amount of amoxicillin and potassium clavulanate such that the amount of amoxicillin is in the range 1400 to 1900 mg, preferably 1500 to 1900 mg, and potassium clavulanate is present in a pro rata amount such that the weight ratio of amoxicillin to clavulanate is from 2:1 to 14:1, preferably 7:1 to 14:1, more preferably 12:1 to 14:1, at intervals of about 12 h, in which the dosage is delivered from a modified release formulation.

As used herein, the term "modified release" refers to a release of drug substance from a pharmaceutical formulation which is at a slower rate than from an immediate release formulation such as a conventional swallow tablet or capsule and may include an immediate release phase and a slow release phase. Modified release formulations are well known in the art, see for instance Remington: The Science and Practice of Pharmacy, Nineteenth Edn, 1995, Mack Publishing Co, Pennsylvania, USA.

Preferably, the modified release formulations of the present invention are formulated such that the release of amoxicillin is effected predominantly through the stomach and small intestine, so that absorption through the specific amoxicillin absorption site in the small intestine is maximised. Preferably, the amoxicillin release profile is made up of a contribution from an immediate release component which is then complemented and extended by an on-going contribution from a slow release component. Preferably, potassium clavulanate is released substantially immediately from the formulation, when the formulation reaches the stomach and is absorbed therefrom, thereby minimising the risk of degradation from prolonged exposure to the stomach. Such formulations are preferably formulated such that the release of amoxicillin and potassium clavulanate occurs predominantly within 3 hours of ingestion of the formulation.

Typically, a dosage will provide 125 mg of potassium clavulanate, the amount approved in existing regimens where a lesser amount of amoxicillin is administered.

Representative modified release dosages include 1500/125, 1750/125 and 2000/125 mg of amoxicillin and potassium clavulanate, respectively. A preferred dosage is 2000/125 mg of amoxicillin and potassium clavulanate.

The dosage in a modified release formulation may conveniently be provided as a number of swallow tablets or capsules, for instance two, three or four, some of which may be the same and some of which may comprise amoxicillin only and no potassium clavulanate. Thus, for instance, a dosage of 2000 mg amoxicillin and 125 mg potassium clavulanate may be provided by two tablets each comprising 1000/62.5 mg amoxicillin/potassium clavulanate, one tablet comprising 1000 mg of amoxicillin and one tablet comprising 1000/125 mg amoxicillin/potassium clavulanate, two tablets each comprising 500 mg amoxicillin and one tablet comprising 1000/125 mg amoxicillin/potassium clavulanate or four tablets each comprising tablet 500/32.25 mg amoxicillin/potassium clavulanate. In addition, a dosage of 1750 mg amoxicillin and 125 mg potassium clavulanate may be provided by two tablets each comprising 875/62.5 mg amoxicillin/potassium clavulanate or one tablet comprising 875 mg of amoxicillin and one tablet comprising 875/125 mg amoxicillin/potassium clavulanate. A preferred tablet comprises 1000/62.5 mg amoxicillin/potassium clavulanate.

The dosage in an modified release formulation may be may also provided as a single tablet. Because of the quantities of drug substance being used , this would preferably be other than a swallow tablet, for instance a dispersible tablet or a chewable tablet which may also be effervescent and/or dispersible or a dispersible tablet. A single unit dosage may also be conveniently provided as a single dosage sachet. It will be appreciated that the dosage may also be provided as a number of smaller non-swallow tablets or sachets, for instance 2 x 1000/62.5 mg or 4 x 500/32.25 mg amoxicillin/potassium clavulanate.

Preferably, in the modified release formulation, all the potassium clavulanate is provided in an immediate release phase whilst amoxicillin is provided in both an immediate release and a slow release phase.

Accordingly, in a further aspect, the present invention provides for a modified release pharmaceutical formulation comprising amoxicillin and potassium clavulanate in the ratio from 2:1 to 20:1, preferably 7:1 to 20:1, more preferably 12:1 to 20:1, most preferably 14:1 to 16:1 in which all of the potassium clavulanate and a first part of amoxicillin are formulated with pharmaceutically acceptable excipients which allow for immediate release of the potassium clavulanate and the first part of amoxicillin, to form an immediate release phase, and further comprising a second part of amoxicillin

formulated with pharmaceutically acceptable excipients which allow for slow release of the second part of amoxicillin, to form a slow release phase.

As used herein, the term "slow release" refers to the gradual but continuous or sustained release over a relatively extended period of the active material content (in this case amoxicillin) after oral ingestion and which starts when the formulation reaches the stomach and starts to disintegrate/dissolve. The release will continue over a period of time and may continue through until and after the formulation reaches the intestine. This can be contrasted with the term "delayed release" in which release of the active does not start immediately the formulation reaches the stomach but is delayed for a period of time, for instance until when the formulation reaches the intestine when the increasing pH is used to trigger release of the active from the formulation.

Preferably, the modified release formulation has an *in vitro* dissolution profile in which 45 to 65%, preferably 45 to 55% of the amoxicillin content is dissolved within 30 min; further in which 50 to 75%, preferably 55 to 65% of the amoxicillin content is dissolved within 60 min; further in which 55 to 85%, preferably 60 to 70% of the amoxicillin content is dissolved within 120 min; further in which 70 to 95%, preferably 75 to 85% of the amoxicillin content is dissolved within 180 min; and further in which 70 to 100%, preferably 75 to 100% of the amoxicillin content is dissolved within 240 min. In comparison, a conventional, immediate release amoxicillin tablet dissolves essentially completely within 30 minutes. The dissolution profile may be measured in a standard dissolution assay, for instance <711> Dissolution Test, Apparatus 2, provided in USP 23, 1995, at  $37.0 \pm 0.5^\circ\text{C}$ , using deionised water (900 mL) and a paddle speed of 75 rpm.

Preferably, the modified release formulation has a biphasic profile *in vivo* with respect to amoxicillin, that is an initial burst from the immediate release phase to provide an acceptable  $C_{\text{max}}$  value, supplemented by a further contribution from the slow release phase, to extend the  $T > \text{MIC}$  parameter to an acceptable value.

Preferably, the modified formulation provides an "Area Under the Curve" (AUC) value which is substantially similar to, for instance at least 80%, preferably at least 90%, more preferably about 100%, of that of the corresponding dosage of amoxicillin taken as a conventional (immediate release) formulation, over the same dosage period, thereby maximising the absorption of the amoxicillin component from the slow release component.

The pharmacokinetic profile for a dosage of the present invention may be readily determined from a single dosage bioavailability study in human volunteers. Plasma

concentrations of amoxicillin may then be readily determined in blood samples taken from patients according to procedures well known and documented in the art.

Representative modified release formulations include a tablet, including swallow tablets, dispersible tablets, chewable tablets which may also be effervescent and/or dispersible and, a capsule, granules or a sachet, typically a swallow tablet.

Representative modified release formulations having an immediate and a slow release phase provide a unit dosage in the range 700 to 1300 mg, preferably, 950 to 1300 mg, amoxicillin, for instance unit dosages of 1000, 875 and 750/62.5 mg amoxicillin/clavulanate. Alternatively, and where the physical size of the dosage form is not a problem, the unit dosage may provide the whole dosage, for instance a single dosage sachet, chewable tablet or dispersible tablet may comprise 1400 to 2600 mg, preferably, 1900 to 2600 mg, amoxicillin, for instance unit dosages of 2000, 1750 and 1500/125 mg amoxicillin/clavulanate. It will be appreciated that such 1000, 875 and 750/62.5 mg formulations are novel.

Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation having an immediate release phase and a slow release phase and comprising:

(a) a unit dosage in the range 700 to 1300 mg, preferably, 950 to 1300 mg, amoxicillin, and a corresponding amount of potassium clavulanate, in a nominal ratio of about 16:1, 14:1 or 12:1, for instance unit dosages of 1000, 875 or 750 mg  $\pm 5\%$  amoxicillin and 62.5 mg  $\pm 5\%$  potassium clavulanate, respectively, or

(b) a unit dosage in the range 1400 to 2600 mg, preferably, 1900 to 2600 mg, amoxicillin, and a corresponding amount of potassium clavulanate, in a nominal ratio of about 16:1, 14:1 or 12:1, for instance unit dosages of 2000, 1750 or 1500 mg  $\pm 5\%$  amoxicillin and 62.5 mg  $\pm 5\%$  potassium clavulanate, respectively, in combination with pharmaceutically acceptable excipients or carriers.

Preferably, the ratio of amoxicillin in the immediate and slow release phases is from 3:1 to 1:3, more preferably, from 2:1 to 2:3, yet more preferably 3:2 to 1:1. Representative ratios include about 2:1, 9:7 or 1:1. It is found useful to employ an excess of amoxicillin in the immediate release phase, to ensure an adequate  $C_{\max}$  value.

In the modified release formulations of the present invention, the portion of amoxicillin which is released immediately may be provided as amoxicillin trihydrate or an alkaline salt thereof, for instance potassium or sodium amoxicillin, preferably, (crystallised) sodium amoxicillin or a mixture thereof, preferably amoxicillin trihydrate; whilst the portion of amoxicillin which is released slowly is provided as amoxicillin

trihydrate or an alkaline salt thereof, for instance potassium or (crystallised) sodium amoxicillin or a mixture thereof, preferably (crystallised) sodium amoxicillin.

5 Preferably, the modified release formulation is a tablet. In a preferred modified release tablet comprising 1000 mg amoxicillin and 62.5 mg potassium clavulanate, the immediate release phase comprises about 563 mg  $\pm 5\%$  amoxicillin trihydrate and about 62.5 mg  $\pm 5\%$  of potassium clavulanate and the slow release phase about 438 mg  $\pm 5\%$  of amoxicillin, preferably as (crystallised) sodium amoxicillin.

10 In a representative modified release tablet of the present invention, the immediate release phase comprises about 438 mg amoxicillin, preferably amoxicillin trihydrate and about 62.5 mg of potassium clavulanate and the slow release phase about 438 mg of amoxicillin, preferably (crystallised) sodium amoxicillin, providing overall an 875/62.5 mg (14:1) tablet.

15 In a further representative tablet of the present invention, the immediate release phase comprises about 500 mg amoxicillin and about 62.5 mg of potassium clavulanate and the slow release phase about 250 mg of amoxicillin, preferably (crystallised) sodium amoxicillin, providing overall a 750/62.5 mg (12:1) tablet.

It will be appreciated that the use of a mixture of amoxicillin trihydrate and sodium amoxicillin is more generally applicable to other pharmaceutical formulations comprising amoxicillin and potassium clavulanate.

20 Accordingly, in a further aspect, the present invention provides for a pharmaceutical formulation comprising amoxicillin and potassium clavulanate in a ratio of from 1:1 to 30:1, preferably 2:1 to 20:1, more preferably 12:1 to 20:1, yet more preferably 14:1 to 16:1, in which amoxicillin is provided as a mixture of amoxicillin trihydrate and sodium amoxicillin in a ratio of from 3:1 to 1:3, more preferably from 2:1  
25 to 2:3, yet more preferably 3:2 to 1:1. Preferably, sodium amoxicillin is crystallised sodium amoxicillin. Representative formulation types include tablets, including immediate release and modified release tablets as herein described, as well as other solid dosage forms such as capsules, single dosage sachets and granules. Representative tablets include those comprising 1000, 875, 500 and 250 mg amoxicillin and a  
30 corresponding weight of potassium clavulanate. Representative ratios include 4:1, 7:1, 8:1, 14:1, and 16:1 (amoxicillin :clavulanate). Preferably, in modified release formulations of the present invention, the amoxicillin in the immediate release phase consists essentially of amoxicillin trihydrate and the amoxicillin of the slow release phase consists essentially of sodium amoxicillin.

35 For a tablet formulation, the immediate and slow release phases may be provided in a number of different formats.

In a preferred aspect, the immediate and slow release phases are provided as separate layers of a layered tablet.

Accordingly, in a further aspect, the present invention provides for a layered tablet formulation comprising potassium clavulanate and amoxicillin in an immediate release layer phase and amoxicillin in a slow release layer. The layered tablet may have two layers, or two layers plus one or more barrier layer, as well as a coating layer. As used herein, the term "bilayer" tablet refers to a tablet consisting of an immediate release and a slow release layer, optionally with a coating layer.

An immediate release layer may be, for example, a layer which disintegrates immediately or rapidly and has a composition similar to that of known tablets which disintegrate immediately or rapidly. For example, the layer may comprise, in addition to the active material content, excipients including diluents such as microcrystalline cellulose; disintegrants such as cross-linked polyvinylpyrrolidone (CLPVP), sodium starch glycollate; compression aids such as colloidal silicon dioxide and microcrystalline cellulose; and lubricants such as magnesium stearate. Such an immediate release layer may comprise around 60 to 85 % (all percentages given herein are on a weight percentage basis unless otherwise stated), preferably 70 to 85 %, of active material content, around 10 to 30 %, preferably 10 to 20 % of fillers/compression aids, and conventional amounts of disintegrants and lubricants, typically about 0.5 to 3%, etc.

An alternative type of immediate release layer may be a swellable layer having a composition which incorporates polymeric materials which swell immediately and extensively in contact with water or aqueous media, to form a water permeable but relatively large swollen mass. Active material content may be immediately leached out of this mass.

Slow release layers have a composition which comprises amoxicillin together with a release retarding excipient which allows for slow release of amoxicillin. Suitable release retarding excipients include pH sensitive polymers, for instance polymers based upon methacrylic acid copolymers such as the Eudragit (trade mark) polymers, for example Eudragit L (trade mark) which may be used either alone or with a plasticiser; release-retarding polymers which have a high degree of swelling in contact with water or aqueous media such as the stomach contents; polymeric materials which form a gel on contact with water or aqueous media; and polymeric materials which have both swelling and gelling characteristics in contact with water or aqueous media.

Release retarding polymers which have a high degree of swelling include, *inter alia*, cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide, potassium

methacrylatedivinylbenzene co-polymer, polymethylmethacrylate, cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols etc.

Release retarding gellable polymers include methylcellulose, carboxymethylcellulose, low-molecular weight hydroxypropylmethylcellulose, low-molecular weight polyvinylalcohols, polyoxyethyleneglycols, non-cross linked polyvinylpyrrolidone, xanthan gum etc.

Release retarding polymers simultaneously possessing swelling and gelling properties include medium-viscosity hydroxypropylmethylcellulose and medium-viscosity polyvinylalcohols.

A preferred release-retarding polymer is xanthan gum, in particular a fine mesh grade of xanthan gum, preferably pharmaceutical grade xanthan gum, 200 mesh, for instance the product Xantural 75 (also known as Keltrol CR, Trade Mark, Monsanto, 800 N Lindbergh Blvd, St Louis, MO 63167, USA). Xanthan gum is a polysaccharide which upon hydration forms a viscous gel layer around the tablet through which the active has to diffuse. It has been shown that the smaller the particle size, the slower the release rate. In addition, the rate of release of drug substance is dependent upon the amount of xanthan gum used and can be adjusted to give the desired profile. Controlled release formulations comprising from 7.5 to 25% xanthan gum are described in EP 0 234 670-A (Boots Co plc). The preferred embodiment is a tablet comprising ibuprofen as the drug substance and 15-20% xanthan gum, which is taken once daily.

Examples of other polymers which may be used include Methocel K4M (Trade Mark), Methocel E5 (Trade Mark), Methocel E5O (Trade Mark), Methocel E4M (Trade Mark), Methocel K15M (Trade Mark) and Methocel K100M (Trade Mark). An example of a suitable polymer mixture is a mixture of Methocel E5 and K4M, for example 1:1, w:w.

Other known release-retarding polymers which may be incorporated include hydrocolloids such as natural or synthetic gums, cellulose derivatives other than those listed above, carbohydrate-based substances such as acacia, gum tragacanth, locust bean gum, guar gum, agar, pectin, carageenin, soluble and insoluble alginates, carboxypolymethylene, casein, zein, and the like, and proteinaceous substances such as gelatin.

Such a slow release layer may contain polymers which immediately swell in contact with water or aqueous media so that they form a relatively large swollen mass which is not immediately discharged from the stomach into the intestine.

The slow release layer may also include diluents such as lactose; compression aids such as microcrystalline cellulose; and lubricants such as magnesium stearate. The

slow release layer may further comprise disintegrants, such as cross-linked polyvinylpyrrolidone (CLPVP) and sodium starch glycollate; binders such as povidone (polyvinylpyrrolidone); desiccants, such as silicon dioxide; and soluble excipients such as mannitol or other soluble sugars. Typically, the slow release layer comprises from about 60 to 80% by weight of amoxicillin; from 10 to 20 % by weight of diluent/compression aid and from 1 to 2.5 % by weight of lubricant.

When xanthan gum is used as release-retarding polymer, the layer contains from 60 to 80% of amoxicillin, 4 to 25%, preferably 4 to 15%, more preferably 5 to 15%, typically about 6 to 10%, of xanthan gum, from 10 to 30%, preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 70 to 80% of amoxicillin, from 4 to 10%, of xanthan gum, from 10 to 20% of microcrystalline cellulose, and from 1 to 2.5 % of magnesium stearate, all % being by weight of the layer.

When release-retarding polymers other than xanthan gum are used, the slow release layer may contain around 30 to 70%, preferably from 40 to 60%, of amoxicillin, from 15 to 45% of release-retarding polymer, from 0 to 30% of fillers/compression aids, conventional quantities of lubricants, and from 5 to 20% of soluble excipients, all % being by weight of the layer.

It has also been surprisingly found that when the amoxicillin in the slow release layer is in the form of a soluble salt thereof, such as sodium amoxicillin, then the release thereof may be retarded by the inclusion of an organic acid.

Accordingly, in a further aspect, the present invention provides for the use of a pharmaceutically acceptable organic acid as a release retarding excipient in a formulation comprising a pharmaceutically acceptable soluble salt of amoxicillin, for instance sodium or potassium amoxicillin, preferably sodium amoxicillin.

It will be appreciated that the use of an organic acid as a release retarding excipient is more generally applicable beyond the particular formulations hereinbefore described.

Accordingly, the present invention further provides for a pharmaceutical formulation comprising a pharmaceutically acceptable soluble salt of amoxicillin, for instance sodium amoxicillin, in a slow release phase which further comprises a release retarding excipient which is a pharmaceutically acceptable organic acid present in a molar ratio of from 100:1 to 1:10, preferably 50:1 to 1:5, more preferably 20:1 to 1:2 (amoxicillin to organic acid).

It is believed that intimate contact between the organic acid and the salt of amoxicillin in the pharmaceutical formulation, for instance as a consequence of

compacted granule formation or direct compression in a tablet, causes some form of interaction which modifies the release of the amoxicillin component from the formulation.

5 Soluble pharmaceutically acceptable salts of amoxicillin include alkali metal salts such as sodium and potassium; alkaline earth metal salts such as magnesium and calcium, and acid salts such as amoxicillin hydrochloride. Preferably, the salt is sodium amoxicillin, more preferably crystalline sodium amoxicillin.

10 As used herein, the term "pharmaceutically acceptable organic acid" refers to organic acids which are without pharmacological effect *per se*, have acceptable organoleptic properties, have acceptable density, do not have an extreme pH and are preferably solid. Examples thereof include mono-carboxylic acids and poly-carboxylic acids having from 2 to 25, preferably from 2 to 10, carbon atoms; monocyclic and polycyclic aryl acids such as benzoic acid; as well as monohydrogen, dihydrogen etc metal salts of multi-valent acids. A single pharmaceutically acceptable organic acid may  
15 be used, or two or more of such may be used in combination. Preferably, the organic acid is a C<sub>(2-10)</sub>alkyl- or alkenyl- carboxylic acid having from one, two or three carboxylic acid groups, and optionally with one or more hydroxy substituents or an additional CO group in the carbon chain, for instance malonic acid, succinic acid, fumaric acid, maleic acid, adipic acid, lactic acid, levulinic acid, sorbic acid or a fruit  
20 acid such as tartaric acid, malic acid, ascorbic acid or citric acid, or an acidic salt thereof, more preferably citric acid.

The organic acid may be used alone or in combination with a release retarding polymer as hereinbefore described. A preferred combination comprises citric acid and a release retarding gellable polymer, in particular xanthan gum. In the presence of the  
25 organic acid, for instance citric acid, xanthan gum may be used at a lower level than when included on its own, for instance, from 0.5 to 8%, preferably 1 to 5%, typically about 2%, by weight of the slow release layer.

When an organic acid is used as a release-retarding excipient, the slow release layer contains from 60 to 80% of a soluble salt of amoxicillin, from 10 to 30%,  
30 preferably 10 to 20% of fillers/compression aids, and conventional quantities of lubricants, all % being by weight of the layer. In a preferred embodiment, the slow release layer comprises from 60 to 70 % of a soluble salt of amoxicillin, from 10 to 20% of microcrystalline cellulose, and from 1 to 2.5 % of magnesium stearate, all % being by weight of the layer.

35 In a representative example, a layered tablet comprises in the slow release layer crystallised sodium amoxicillin and citric acid, in a molar ratio of about 50:1 to 1:2,

preferably 20:1 to 1:2, more preferably 2:1 to 1:1.2, yet more preferably about 1:1. In a preferred embodiment, the slow release layer comprises about 438 mg  $\pm 5\%$  crystallised sodium amoxicillin, about 78 mg  $\pm 10\%$  citric acid and about 2% by weight of xanthan gum.

5 In a preferred layered tablet comprising 1000 mg amoxicillin and 62.5 mg potassium clavulanate, the immediate release layer comprises about 563 mg  $\pm 5\%$  amoxicillin, preferably amoxicillin trihydrate, and about 62.5 mg  $\pm 5\%$  of potassium clavulanate and the slow release layer about 438 mg  $\pm 5\%$  of amoxicillin, preferably crystallised sodium amoxicillin, about 78 mg  $\pm 10\%$  citric acid and about 2% by weight  
10 of xanthan gum.

The tablet formulations of the invention may also include one or more barrier layers, which may be located between the respective first and second layers, and/or on one or more of the outer surfaces of the first and second layers, for example the end faces of the layers of a substantially cylindrical tablet. Such barrier layers may, for  
15 example, be composed of polymers which are either substantially or completely impermeable to water or aqueous media, or are slowly erodable in water or aqueous media or biological liquids and/or which swell in contact with water or aqueous media. Suitably the barrier layer should be such that it retains these characteristics at least until complete or substantially complete transfer of the active material content to the  
20 surrounding medium.

Suitable polymers for the barrier layer include acrylates, methacrylates, copolymers of acrylic acid, celluloses and derivatives thereof such as ethylcelluloses, cellulose acetate propionate, polyethylenes and polyvinyl alcohols etc. Barrier layers comprising polymers which swell in contact with water or aqueous media may swell to  
25 such an extent that the swollen layer forms a relatively large swollen mass, the size of which delays its immediate discharge from the stomach into the intestine. The barrier layer may itself contain active material content, for example the barrier layer may be a slow or delayed release layer. Barrier layers may typically have an individual thickness of 2 mm to 10 microns.

30 Suitable polymers for barrier layers which are relatively impermeable to water include the Methocel (trade mark) series of polymers mentioned above, for example Methocel K100M, Methocel K15M, Methocel E5 and Methocel E50, used singly or combined, or optionally combined with an Ethocel (trade mark) polymer. Such polymers may suitably be used in combination with a plasticiser such as hydrogenated  
35 castor oil. The barrier layer may also include conventional binders, fillers, lubricants

and compression acids etc such as Polyvidon K30 (trade mark), magnesium stearate, and silicon dioxide, e.g. Syloid 244 (trade mark).

5 The tablet formulation of the invention may be wholly or partly covered by a coating layer, which may be a protective layer to prevent ingress of moisture or damage to the tablet. The coating layer may itself contain active material content, and may, for example, be an immediate release layer, which immediately disintegrates in contact with water or aqueous media to release its active material content, for example amoxicillin and potassium clavulanate. Preferred coating materials comprise hydroxypropylmethylcellulose and polyethylene glycol, with titanium dioxide as an opacifying agent, for instance as described in WO 95/28927 (SmithKline Beecham).

10 As well as active material content etc, the tablet of the invention may also include a pH modifying agent, such as a pH buffer, which may be contained in either the immediate-, or slow-release layers, or in a coating around all or part of the tablet. A suitable buffer is calcium hydrogen phosphate.

15 In a tablet without a barrier layer, the immediate release layer comprises from 50 to 60% and the slow release layer comprises from 40 to 50% of the overall tablet weight. When a barrier layer is present, the immediate release layer typically comprises from 40 to 50%, the slow release layer comprises from 35 to 45%, and the barrier layer comprises from 5 to 20% of the overall tablet weight.

20 It is found that a satisfactory pharmacokinetic profile may be obtained from a bilayered tablet of the present invention without the need to include a barrier layer. Accordingly, a bi-layer tablet is preferred. This also reduces the complexity of the manufacturing process.

25 It will be appreciated that 1000, 875 and 750/62.5 mg layered tablets having an immediate release layer and a slow release layer are novel. Accordingly, in a further aspect, the present invention provides for a pharmaceutical layered tablet formulation comprising an immediate release layer and a slow release layer and comprising from 700 to 1250 mg amoxicillin and a pro rata amount of potassium clavulanate, preferably 1000, 875 or 750 mg  $\pm 5\%$  amoxicillin and 62.5 mg  $\pm 5\%$  potassium clavulanate, in a nominal ratio of about 16:1, 14:1 or 12:1, respectively, in combination with pharmaceutically acceptable excipients or carriers. Preferably, the layered tablet is a bi-layered tablet.

30 Suitably the tablet formulations of the invention may be formed by known compression tableting techniques, for example using a known multi-layer tableting press. Preferably, in a preliminary step, slugging or roller compaction is used to form granulates. Lubricants and compression aids (if used) are then added, to form a compression blend for subsequent compaction.

Preferred bilayer tablets of the present invention may be made by a process which comprises, as an early phase, the formation of slow release compacted granules, comprising the steps of milling sodium amoxicillin, a portion of the diluent/compression aid such as microcrystalline cellulose (typically about 30%), a portion of the lubricant (typically about 70%) and a pharmaceutically acceptable organic acid such as a fruit acid, for instance citric acid, and then blending with a release retarding polymer such as xanthan gum, if present, and a compression aid such as colloidal silicon dioxide, compacting the blend, for instance in a roller compactor or by slugging, and then milling, to form slow release granules. Preferably such granules have a size in the range 100 to 1000 microns. The incorporation of xanthan gum appears to also have an unexpected benefit on processibility.

Alternatively, slow release granules in which amoxicillin is present as amoxicillin trihydrate and the release modifying excipient is xanthan gum may be prepared by a similar process. Such slow release compacted granules may then be blended with other excipients such as the remaining magnesium stearate and microcrystalline cellulose, to form a slow release compression blend.

In addition, amoxicillin trihydrate, potassium clavulanate (preferably as a 1:1 blend with microcrystalline cellulose), microcrystalline cellulose (a portion of total used), are milled and blended with a lubricant such as magnesium stearate (preferably about 50% of total), and then compacted, for instance in a roller compactor or by slugging, and milled to form immediate release compacted granules. These immediate release compacted granules may then be blended with other excipients such as the remaining magnesium stearate and microcrystalline cellulose (about 13%), a compression aid such as colloidal silica, and a disintegrant such as sodium starch glycolate, to form an immediate release compression blend.

The immediate release and slow release compression blends may then be compressed as separate layers on a bilayer tablet press, to form bilayer tablets.

Such slow release granules are novel. Accordingly, in a further aspect, the present invention provides for compacted granules comprising a soluble salt of amoxicillin, for instance sodium amoxicillin, a diluent/compression aid, and an organic acid or a release retarding polymer or a mixture thereof, as hereinbefore defined. In a yet further aspect, the present invention also provides for compacted granules comprising amoxicillin trihydrate, a diluent/compression aid, and a release retarding polymer, as hereinbefore defined.

Alternatively, a dry densification process may be used, e.g. briquetting. Typically the active material content, pH modifiers, buffers, fillers and/or diluent, release

retarding agents, disintegrants and binders, when used are mixed, then lubricants and compression aids are added. The complete mixture may then be compressed under high pressure in the tablet press. A wet granulation process may be also be used, for instance with isopropanol as the solvent and Polyvidon K-30 (trade mark) as the wet granulating aid.

5 A barrier layer, if present, may typically be made up by a wet granulation technique, or by dry granulation techniques such as roller compaction. Typically the barrier material, e.g. Methocel (trade mark) is suspended in a solvent such as ethanol containing a granulation acid such as Ethocel or Polyvidon K-30 (trade mark), followed  
10 by mixing, sieving and granulation. Typically a first layer may be formed, then a barrier layer deposited upon it, e.g. by compression, spraying or immersion techniques, then the second layer may be formed so that the barrier layer is sandwiched between the first and second layers. Additionally, or alternatively, the first and second layers may be formed and a barrier layer may then be formed, for instance by compression, spraying or  
15 immersion, on one or more of the end faces of the tablet.

A process for the preparation of crystallised sodium amoxicillin is described in EP-A-0 131 147 (Beecham Group plc).

Potassium clavulanate is known to be extremely water sensitive. Therefore tablet formulations which contain potassium clavulanate should be made up in dry conditions,  
20 preferably at 30% relative humidity or less, and the ingredients of the formulation should be pre-dried where appropriate. Tablet formulations of the invention should be stored in containers which are sealed against the ingress of atmospheric moisture.

Tablet cores may then be coated with a coating layer which may be applied form an aqueous or an organic solvent system, preferably an aqueous solvent system, to  
25 provide film coated tablets.

The invention also provides a method for the manufacture of a tablet formulation as described above comprising the steps of forming said first and second layers, and any barrier layers and coating layer(s) which may be present.

In addition to the layered tablet approach hereinbefore described, other types of  
30 tablet may be used to provide an immediate release phase and a slow release phase, using the excipients hereinbefore described but providing the phases in different formats. Thus, the slow release phase may form the core of a tablet which is then surrounded by an outer casing forming the immediate release phase, optionally with an intermediate coating layer around the core and/or a final coating layer around the outer casing (see  
35 WO 95/28148, SmithKline Beecham). The slow release phase may also be provided as

granules which are dispersed in a matrix of amoxicillin and potassium clavulanate, the matrix forming the immediate release phase (see WO 96/04908, SmithKline Beecham).

In a further variant, a monolith modified release tablet may be prepared from slow release compacted granules comprising amoxicillin, a diluent/compression aid such as microcrystalline cellulose, and a pharmaceutically acceptable organic acid such as a fruit acid, for instance citric acid (if amoxicillin is present as a soluble salt thereof), or a release retarding polymer such as xanthan gum or a mixture thereof, preferably a release retarding polymer (as hereinbefore described); and immediate release compacted granules comprising amoxicillin and potassium clavulanate (as hereinbefore described) or immediate release compacted granules comprising amoxicillin and potassium clavulanate, for instance in a 2:1 ratio, and further immediate release compacted granules comprising amoxicillin (as described in WO 98/35672, SmithKline Beecham Laboratoires Pharmaceutiques), the granules being combined with extragranular excipients to form tablets. Such granules may also be processed into other pharmaceutical formulations, for instance single dosage sachets, capsules or chewable tablets comprising a unit dosage as hereinbefore described.

Chewable tablets according to the present invention typically comprise a chewable base formed from, for instance, mannitol, sorbitol, dextrose, fructose or lactose alone or in combination. A chewable tablet may also comprise further excipients, for instance, disintegrants, lubricants, sweetening agents, colouring and flavouring agents. Such further excipients together will preferably comprise from 3 to 10%, more preferably 4 to 8%, yet more preferably 4 to 7% by weight of the tablet. Disintegrants may be present in from 1 to 4%, preferably from 1 to 3%, more preferably from 1 to 2% by weight of the tablet. Representative disintegrants include croscopovidone, sodium starch glycollate, starches such as maize starch and rice starch, croscarmellose sodium and cellulose products such as microcrystalline cellulose, microfine cellulose, low substituted hydroxy propyl cellulose, either used singly or in admixture. Preferably, the disintegrant is croscopovidone. Lubricants may be present in from 0.25 to 2.0%, preferably from 0.5 to 1.2% by weight of the tablet. Preferred lubricants include magnesium stearate. Preferably, the sweetening agent is an artificial sweetening agent such as sodium saccharin or aspartame, preferably aspartame, which may be present in from 0.5 to 1.5% by weight of the tablet. Preferably, a tablet of the present invention is substantially free of sugar (sucrose). Preferred flavouring agents include fruit flavours which may be natural or synthetic, for instance peppermint, cherry and banana, or a mixture thereof.

Single dose sachets according to the present invention comprise, in addition to the drug substance, excipients typically included in a sachet formulation, such as a sweetener, for instance aspartame, flavourings, for instance fruit flavours, optionally a suspending agent such as xanthan gum, as well as silica gel, to act as a desiccant.

5 Capsules according to the present invention comprise, in addition to the drug substance, excipients typically included in a capsule, for instance starch, lactose, microcrystalline cellulose, magnesium stearate. It will be appreciated that due to the hygroscopic nature of clavulanate, the use of materials such as gelatin for forming the capsules should be avoided. Preferably, capsules are prepared from materials such as  
10 HPMC or a gelatin/PEG combination.

In a further embodiment, the slow release phase may be provided as a separate component, for instance as a separate tablet, so that the unit dosage is provided as a combination of a conventional component in which amoxicillin and potassium clavulanate are released immediately, optionally with a conventional amoxicillin  
15 formulation such as a tablet, and a further formulation, for instance a tablet, comprising amoxicillin (and no potassium clavulanate) from which amoxicillin is released slowly. The weight of potassium clavulanate and the combined weights of amoxicillin in the conventional and slow release formulations will provide the overall unit dosage. Thus, for instance a dosage of 2000/125 mg may be provided by a combination of an existing  
20 500/125 mg amoxicillin/potassium clavulanate tablet and a 500 mg amoxicillin tablet in combination with a slow release tablet comprising 1000 mg of amoxicillin. Furthermore, a dosage of 1750/125 mg may be provided by an existing 875/125mg tablet (as described in WO 95/28927, SmithKline Beecham) in combination with a slow release tablet comprising 875 mg of amoxicillin. In addition, a dosage of 1500/125 mg  
25 may be provided by an existing 500/125 mg tablet and an existing 500 mg tablet of amoxicillin in combination with a slow release tablet comprising 500 mg of amoxicillin. Accordingly, in a further aspect, the present invention provides for a kit comprising a conventional (immediate release) tablet comprising amoxicillin and potassium clavulanate, optionally with a conventional (immediate release) tablet comprising  
30 amoxicillin, and a slow release tablet comprising amoxicillin (and no potassium clavulanate).

In a further aspect, the present invention provides for a pharmaceutical formulation, preferably a tablet, comprising amoxicillin (as the sole active ingredient) formulated with a release retarding excipient which causes a slow release of the  
35 amoxicillin from the formulation, and excluding; tablets which comprise 750 mg or less of amoxicillin in which the amoxicillin is present essentially as amoxicillin trihydrate; or

tablets comprising from 400 to 500 mg amoxicillin in which amoxicillin is present as a mixture comprising at least 70% amoxicillin trihydrate and up to 30% sodium amoxicillin in combination with hydroxypropyl methylcellulose as a release retarding excipient.

5        Such formulations may comprise from 100 to 1250 mg amoxicillin which may be amoxicillin trihydrate or (crystallised) sodium amoxicillin or a mixture thereof, for instance 500, 875 or 1000 mg amoxicillin. Suitable excipients for slow release are those hereinbefore described for slow release layers. The formulation may comprise from 4 to 25%, preferably from 4 to 15%, more preferably 4 to 10% of xanthan gum, or from 10 to 10 25, preferably 15 to 20% of a hydroxypropyl-methylcellulose, for instance Methocel K100LV or Methocel K4M. Alternatively, such formulations may comprise citric acid, optionally with xanthan gum, as hereinbefore described.

15        The modified release formulations of the present invention are intended for use in a bid dosing regimen. It will be appreciated that whilst such a bid dosing regimen is recognised to offer the advantage of greater convenience and therefore likely greater compliance, in some instances, it may be preferred to use administer the same total daily dosage but in a tid regimen, that is in equally divided doses every 8 hours, rather than every 12 hours. Accordingly, in a further aspect, the 20 present invention provides for a method of treating bacterial infections in humans which comprises orally administering thereto a therapeutically effective amount of amoxicillin and potassium clavulanate such that the amount of amoxicillin is in the range 1250 to 1750 mg, preferably 1300 to 1700 mg, and the amount of potassium clavulanate is such that the weight ratio of amoxicillin to clavulanate is from 2:1 to 25 20:1, preferably 7:1 to 20:1, more preferably 14:1 to 20:1, at intervals of about 8 h, in which the dosage is delivered from a modified release formulation.

Preferably, the dosage regimen provides a mean plasma concentration of amoxicillin of 4 µg/mL for at least 3.0 h, preferably at least 3.2 h, more preferably at least 3.6 h, most preferably for about 4 h or longer.

30        More preferably, the dosage regimen provides a mean plasma concentration of amoxicillin of 8 µg/ml for at least 3.0 h, more preferably at least 3.2 h, most preferably at least 3.6 h.

Preferably, the dosage regimen provides a mean maximum plasma concentration ( $C_{max}$ ) of amoxicillin which is at least 8 µg/mL, preferably at least 35 12 µg/mL, yet more preferably at least 14 µg/mL, most preferably at least 16 µg/mL.

A preferred dosage is in the range 1300 to 1700 mg amoxicillin and 125 mg potassium clavulanate, more preferably 1400 to 1600 mg amoxicillin and 125 mg potassium clavulanate.

Such a dosage may be provided by one or two modified release pharmaceutical formulations, in particular two bilayer or monolith swallow tablets each comprising half the dosage (for instance, 650 to 850 mg amoxicillin, more preferably 700 to 800 mg amoxicillin, and 62.5 mg potassium clavulanate) or a larger chewable tablet or single dose sachet comprising the entire unit dosage (for instance, 1300 to 1700 mg amoxicillin, more preferably 1400 to 1600 mg amoxicillin, and 125 mg potassium clavulanate), by appropriate adjustment to the corresponding formulations hereinbefore described. A representative tablet comprises 750 mg of amoxicillin and 62.5 mg of potassium clavulanate, having a nominal ratio of amoxicillin : potassium clavulanate of 12:1. Such a tablet may comprise from 300 to 450 mg of amoxicillin in the immediate release phase and from 300 to 450 mg of amoxicillin in the slow release phase, to make a total of 750 mg amoxicillin. A further representative tablet comprises 675 mg of amoxicillin and 62.5 mg of potassium clavulanate. Such a tablet may comprise from 250 to 400 mg of amoxicillin in the immediate release phase and from 250 to 400 mg of amoxicillin in the slow release phase, to make a total of 675 mg amoxicillin.

It will be further appreciated that the methods and formulations hereinbefore described for amoxicillin and clavulanate are also applicable to amoxicillin alone, with no clavulanate, particularly for treating infections where  $\beta$ -lactamase producing pathogens are not implicated, for instance infections caused by the organism *Streptococcus pyogenes*, such acute bacterial tonsillitis and/or pharyngitis. The present invention also all such uses and formulations of amoxicillin as the sole agent.

Preferably, the unit dosage forms of the present invention are packaged in containers that inhibit the ingress of atmospheric moisture, for instance blister packs, tightly closed bottles or desiccated pouch packs etc which are conventional in the art. Preferably, bottles also include a desiccating material, to preserve the clavulanate. Preferred bottles include HDPE bottles. Preferred blister packs include cold-formed blister packs in which each blister may contain one tablet, or two tablets, where the unit dosage is two tablets, for instance 2 x 1000/62.5 mg tablets, to improve patient compliance.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent  
5 application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

The invention will now be described by way of example.

**Examples**

- 5 The foregoing examples describe tablet formulations which comprise potassium clavulanate. This is known to be extremely water sensitive. Therefore such tablet formulations should be made up in dry conditions, preferably at 30% relative humidity or less, and the ingredients of the formulation should be pre-dried where appropriate.

**Example 1 – 1000/62.5 mg modified release tablet**

| <b>Ingredient</b>                      | <b>mg/tablet</b> | <b>% w/w</b> |
|--|------------------|--------------|
| <b>Immediate Release Layer</b>         |                  |              |
| Amoxicillin Trihydrate (ERH < 40%)     | 654.1*           | 40.88        |
| Potassium Clavulanate                  | 76.2#            | 4.76         |
| Microcrystalline Cellulose             | 136.4            | 8.52         |
| Sodium Starch Glycollate               | 18.0             | 1.12         |
| Colloidal Silicon Dioxide              | 6.3              | 0.39         |
| Magnesium Stearate                     | 9.0              | 0.56         |
| Total (Immediate Release Layer)        | 900.0            | 56.23        |
| <b>Slow Release Layer</b>              |                  |              |
| Crystallised Sodium Amoxicillin        | 480.8**          | 30.05        |
| Microcrystalline Cellulose             | 113.2            | 7.08         |
| Xanthan Gum                            | 14.0             | 0.87         |
| Citric Acid                            | 78.0             | 4.87         |
| Colloidal Silicon Dioxide              | 1.50             | 0.08         |
| Magnesium Stearate                     | 14.0             | 0.87         |
| Total (Sustained Release Layer)        | 700.0            | 43.74        |
| <b>Film coat</b>                       |                  |              |
| Opadry YS-1-7700 – Composition:        |                  |              |
| Hydroxypropylmethylcellulose 2910 6cp  | 11.6             |              |
| Hydroxypropylmethylcellulose 2910 15cp | 3.9              |              |
| Titanium dioxide                       | 15.1             |              |
| Polyethylene Glycol 3350               | 2.3              |              |
| Polyethylene Glycol 8000               | 2.3              |              |
| Total weight of coated tablet          | 1635.2           |              |

- 10 \* Equivalent to 562.5 mg of amoxicillin based on an assay of 86.0%  
 # Equivalent to 62.5 mg of clavulanic acid based on an assay of 82.0%  
 \*\*Equivalent to 437.5 mg amoxicillin based on an assay of 91.0%

**Example 2 – 1000/62.5 mg modified release tablet** The immediate release layer and film coat are as for the tablet of Example 1

| Ingredient                      | mg/tablet | % w/w |
|---------------------------------|-----------|-------|
| <b>Slow Release Layer</b>       |           |       |
| Crystallised Sodium Amoxicillin | 480.8**   | 30.05 |
| Microcrystalline Cellulose      | 127.2     | 7.95  |
| Citric Acid                     | 78.0      | 4.87  |
| Colloidal Silicon Dioxide       | 1.5       | 0.09  |
| Magnesium Stearate              | 14.0      | 0.87  |
| Total (Slow Release Layer)      | 700.0     | 43.74 |

Total Weight of coated tablet 1635.2

\*\*Equivalent to 437.5 mg amoxicillin based on an assay of 91.0%

### Preparation of modified release tablets

Modified release tablets were prepared according to the process flow diagram shown in Figure 2. In brief, immediate and modified release blends are prepared which involve initial sieving and milling, as indicated, before roller compaction in a Chilsonator and further milling, sieving and blending. The two containers comprising amoxicillin trihydrate and the two containers comprising sodium amoxicillin comprise about equal weights of amoxicillin trihydrate and sodium amoxicillin, respectively.

For the IR blend, the Chilsonator settings were: roll size, width = 4 inches, diam = 10 inches; hydraulic pressure = 900-1100 psi, air pressure = 25-35 psi, roll speed = 15-25 rpm, horizontal auger speed = 15-30 rpm, vertical auger speed = 300-350 rpm.

For the SR blend, the Chilsonator settings were: roll size, width = 4 inches, diam = 10 inches; hydraulic pressure = 500-700 psi, air pressure = 15-20 psi, roll speed = 15-25 rpm, horizontal auger speed = 30-35 rpm, vertical auger speed = 300-350 rpm.

The two blends were then compressed as separate layers in a bilayer tablet press equipped with punches measuring 0.0406 inches by 0.8730 inches and having a modified capsule shape. For the first (immediate release) layer, there was no pre-compression, and a main compression of less than 10 KN. For the second layer, there was a pre-compression of less than 20 KN, and a main compression of less than 60 KN. The tablets thus produced had a total weight of 1600 mg  $\pm$  48 mg, a hardness in the range 8 to 18 SCU and a friability of less than 0.5%.

Finally, the tablet cores were coated with an aqueous film coating, using a 15% solids aqueous suspension, in a 60 inch coating pan which could accommodate up to 300 kg charge of tablets. The pan was equipped with 4 spray guns and rotated at 3 to 5 rpm. The inlet air was dehumidified with the temperature in the range 56 to 60°C whilst the

exhaust air humidity was in the range 4 to 12% and the temperature in the range 43 to 50°C. The spray rate was 80 to 120 ml/min/spray gun.

### Example 3 - Slow release tablet (875 mg)

#### (a) Sodium Amoxicillin Tablet

|                                      | mg/tablet   | %           |
|--------------------------------------|-------------|-------------|
| Crystallised Sodium Amoxicillin 91%* | 961.54      | 73.96       |
| Dried Microcrystalline Cellulose     | 273.46      | 21.04       |
| Magnesium Stearate                   | 13.0        | 1.00        |
| Xanthan gum 200 mesh**               | 52.0        | 4.00        |
| <b>Total</b>                         | <b>1300</b> | <b>1.00</b> |

#### (b) Sodium Amoxicillin Tablet with citric acid

|                                      | mg/tablet   | %          |
|--------------------------------------|-------------|------------|
| Crystallised Sodium Amoxicillin 91%* | 961.54      | 66.31      |
| Dried Microcrystalline Cellulose     | 288.96      | 19.92      |
| Magnesium Stearate                   | 14.50       | 1.00       |
| Citric acid                          | 156         | 10.75      |
| Xanthan gum 200 mesh**               | 29.0        | 2.00       |
| <b>Total</b>                         | <b>1450</b> | <b>100</b> |

#### 10 (c) Amoxicillin Trihydrate Tablet

|                                  | mg/tablet   | %          |
|----------------------------------|-------------|------------|
| Amoxicillin Trihydrate 86%*      | 1017.4      | 78.26      |
| Dried Microcrystalline Cellulose | 217.6       | 16.74      |
| Magnesium Stearate               | 13.0        | 1.00       |
| Xanthan Gum, 200 mesh**          | 52.0        | 4.00       |
| <b>Total</b>                     | <b>1300</b> | <b>100</b> |

\* adjusted for the potency of the amoxicillin component and corresponding to 875 mg amoxicillin,

\*\* Xantural 75

### Example 4 – 875/62.5 mg modified release tablet

#### Slow release layer

This may be formed using half the quantities given above, for a slow release layer comprising about 438 mg amoxicillin.

**Immediate release layer – 1**

|   |   |        |
|---|---|--------|
|   | Amoxicillin trihydrate                    | 507 mg |
|   | (equiv to amoxicillin free acid)          | (438)  |
|   | Potassium clavulanate                     | 71.8   |
| 5 | (equivalent to clavulanic acid)           | (62.5) |
|   | Microcrystalline cellulose (Avicel PH102) | 125    |
|   | Sodium starch glycollate (Explotab)       | 26     |
|   | Magnesium stearate                        | 6.5    |

10 The immediate release layer comprises nominally 438/62.5mg amoxicillin/clavulanate.

**Immediate release layer - 2**

|    |   |        |
|----|---|--------|
|    | Amoxicillin trihydrate                    | 507mg  |
|    | (equiv to amoxicillin free acid)          | (438)  |
| 15 | Potassium clavulanate                     | 71.8   |
|    | (equivalent to clavulanic acid)           | (62.5) |
|    | Microcrystalline cellulose (Avicel PH102) | 135    |
|    | Sodium starch glycollate (Explotab)       | 34     |
|    | Talc                                      | 67     |
| 20 | Magnesium stearate                        | 25     |
|    | Silica (Syloid)                           | 17     |

The immediate release layer comprises nominally 438/62.5mg amoxicillin/clavulanate.

**25 Barrier Layers**

Barrier layers and methods for their preparation are described in WO 95/20946 (SmithKline Beecham) whose disclosure is incorporated herein by reference in its entirety.

**30 Preparation of Tablets**

The active ingredients, fillers and diluents (microcrystalline cellulose), release controlling agents (if present), disintegrants (croscopovidone, sodium starch glycollate) etc are mixed. Lubricants (talc, Mg-stearate) and colloidal silicon dioxide (Syloid 244) are added, and mixing is continued for another minute. The complete mixture is slugged on a tablet press or roller compacted (briquetting step), followed by size reduction (Apex, Fitzmill, Frewitt) and passage through an oscillatory sieve or particle size classifier

(Kason, Sweco). If the flow properties are unsatisfactory, the briquetting step is repeated. Separate compressed blends are prepared for the immediate and slow release layers, and barrier layer, if present.

- 5 In some cases, where the bulk density is rather low, a densifying step (pre-tabletting and sieving as in the briquetting method) may be required in order to achieve the nominal weight of a particular layer.

The blends are then compressed as separate layers on a layer tablet press to form bilayered tablets. Tablets may then be coated with a white opaque coating, for instance the product Opadry, Opaspray (Colorcon).

10

#### Example 5 – 1000 mg monolith tablet

|  | mg/tablet   | %            |
|--|-------------|--------------|
| Crystallised Sodium Amoxicillin <sup>1</sup> | 824.2       | 51.51        |
| Amoxicillin Trihydrate <sup>2</sup>          | 290.7       | 18.17        |
| Clavulanate Potassium <sup>3</sup>           | 76.2        | 4.76         |
| Dried Microcrystalline Cellulose             | 165.9       | 10.37        |
| Magnesium Stearate                           | 23.0        | 1.44         |
| Sodium Starch glycollate                     | 80.0        | 5.00         |
| Colloidal silicon dioxide                    | 6.3         | 0.39         |
| Citric acid                                  | 133.7       | 8.36         |
| <b>Total</b>                                 | <b>1600</b> | <b>100.0</b> |

- 15 <sup>1</sup> adjusted for potency of the amoxicillin component and corresponding to 750 mg of amoxicillin
- <sup>2</sup> adjusted for potency of the amoxicillin component and corresponding to 250 mg of amoxicillin
- <sup>3</sup> adjusted for potency of the clavulanate potassium component and corresponding to 62.5 mg of clavulanate potassium

20

Two separate batches of granules, the first, immediate release granules, comprising amoxicillin and potassium clavulanate and the second, slow release granules, comprising sodium amoxicillin and citric acid, were prepared by roller compaction, as described in Example 2, and then combined with the remaining excipients,

- 25 blended and formed into tablets in a tablet press.

#### Example 6 – 1000 mg monolith tablet

A tablet similar to the tablet of Example 5 may be prepared in which the ratio of amoxicillin trihydrate to sodium amoxicillin is adjusted from 1 : 3 to 9:7 (563/438 mg)

5

**Example 7 – 875 mg slow release tablet**

| Ingredient                 | mg/tablet | % w/w  |
|----------------------------|-----------|--------|
| Sodium Amoxicillin         | 961.5     | 73.96  |
| Microcrystalline Cellulose | 218.5     | 16.81  |
| Xanthan gum                | 97.5      | 7.50   |
| Colloidal Silicon Dioxide  | 3.0       | 0.23   |
| Magnesium Stearate         | 19.5      | 1.50   |
| Total                      | 1300.0    | 100.00 |

\*\*Equivalent to 875 mg amoxicillin based on an assay of 91.0%

10 Slow release tablets were prepared from slow release granules using the process described above in Example 1. The granules were then blended with the remaining ingredients and compressed in a tablet press into tablets.

**Example 8 – 875 mg slow release tablet**

15

A tablet similar to the tablet of Example 7 was prepared in which the level of xanthan gum was increased to 195 mg (15%), with a corresponding reduction in the weight of microcrystalline cellulose.

**Example 9 – 875 mg slow release tablet**

20

A tablet similar to the tablet of Example 7 was prepared in which the sodium amoxicillin was replaced by an equivalent amount of amoxicillin trihydrate (1017.4 mg, 78.26%) with a corresponding reduction in the weight of microcrystalline cellulose

25

**Example 10 - Dissolution Testing Methods**

The release of amoxicillin and clavulanate from tablets into static media was measured using the <711> Dissolution Test, Apparatus 2, provided in USP 23, 1995.

30

**Test specifications:**

|              |                         |
|--------------|-------------------------|
| Temperature: | 37.0 ± 0.5°C            |
| Medium:      | Deionized water, 900 mL |
| Paddle speed | 75 rpm                  |

**Method**

Aliquots of medium were removed for assay after 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420 and 480 min, each aliquot being replaced simultaneously by an equal volume of medium to maintain constant volume. The amount of drug substance was determined by UV spectrometry, at 272nm. The resulting dissolution profile for the tablets of Example 1 and 2 are shown as Fig 3.

**10 *in vivo* Pharmacokinetic evaluation of formulations**

The bioavailability of dosages according to the present invention were evaluated in two human volunteer studies, Study A and Study B. These were open, randomised, crossover studies in healthy volunteers. Each dosage was administered with the aid of approximately 200 mL water, at the start of a light breakfast and after an overnight fast. Blood samples were collected into tubes containing EDTA at nominal times of pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10 and 12 h after start of dosing, for assay of plasma levels of amoxicillin and clavulanate. Samples were cooled in an ice-bath awaiting further processing. Plasma was separated by refrigerated centrifugation at 4°C and transferred to appropriately labelled polypropylene specimen containers and stored frozen at approximately -70°C until assayed.

Samples were assayed for amoxicillin using a method based on protein precipitation with acetonitrile. Amoxicillin was extracted from human plasma (50 µL) by means of protein precipitation, using acetonitrile containing the internal standard and quantified by LC/MS/MS. Specifically, human plasma (50 µL) was pipetted into a 1.5 mL Eppendorf tube followed by the addition of acetonitrile containing the internal standard ([<sup>13</sup>C<sub>6</sub>]-amoxicillin, 200 µL). The tube was capped, vortex mixed and shaken for approximately 15 minutes. After centrifuging the sample (approximately 11,000 x g, for 15 minutes), the supernatant was transferred to a silanised 1.1 mL tapered autosampler vial containing 200 µL of 5mM ammonium acetate solution. An aliquot of extract was injected onto the HPLC/MS/MS system for analysis. The mass spectrometer was operated in positive ion mode, employing a Turbo IonSpray interface. Multiple reaction

monitoring (MRM) was used to detect the components, amoxicillin and [ $^{13}\text{C}_6$ ]-amoxicillin. The MRM procedure involves (1) mass selection of a characteristic ion of the required drug or internal standard in the first quadrupole mass analyser (2) fragmentation of the selected ion in the instrument's collision cell (3) detection of a fragment ion which is characteristic of the compound of interest. Quantification is performed by comparison of the chromatographic peak areas of the drug relative to the area of the internal standard. Linear responses in the analyte/internal standard peak area ratios were observed for analyte concentrations ranging from 0.05  $\mu\text{g/mL}$  (lower limit of quantification; LLQ) to 10  $\mu\text{g/mL}$  (upper limit of quantification: ULQ).

Samples were assayed for clavulanate using a method based on protein precipitation with acetonitrile. Clavulanate was extracted from human plasma by means of liquid/liquid using internal standard and quantified by LC/MS/MS. Specifically, human plasma (50  $\mu\text{L}$ ) was pipetted into a 1.5 mL Eppendorf tube followed by 0.2mM ammonium acetate (200 $\mu\text{L}$ ) before addition of acetonitrile containing the internal standard (6-aminopenicillanic acid, 400  $\mu\text{L}$ ). The tube was capped, vortex mixed and shaken for approximately 20 minutes. After centrifuging the sample (approximately 14,500 x g, for 15 minutes), the supernatant was transferred to a clean eppendorf tube and dichloromethane added. After further mixing and centrifugation (approximately 14,500 x g for 10 minutes) supernatant (no more than 150 $\mu\text{L}$ ) was transferred to a tapered 1.1mL autosampler vial and left uncapped for at least 20 minutes to allow any traces of dichloromethane to evaporate. An aliquot of the extract was injected onto the HPLC/MS/MS system for analysis. The mass spectrometer was operated in positive ion mode, employing a Turbo IonSpray interface. Multiple reaction monitoring (MRM) was used to detect the components, clavulanate and 6-aminopenicillanic acid. The MRM procedure involves (1) mass selection of a characteristic ion of the required drug or internal standard in the first quadrupole mass analyser (2) fragmentation of the selected ion in the instrument's collision cell (3) detection of a fragment ion which is characteristic of the compound of interest. Quantification is performed by comparison of the chromatographic peak areas of the drug relative to the area of the internal standard. Linear responses in the analyte/internal standard peak area ratios were observed for analyte concentrations ranging from 0.05  $\mu\text{g/mL}$  (lower limit of quantification; LLQ) to 10  $\mu\text{g/mL}$  (upper limit of quantification: ULQ).

QC samples were assayed with each batch of samples against separately prepared calibration standards. The results of the QC samples were used to assess the day-to-day performance of the assay.

Plasma concentration-time data for each subject in each regimen were analysed by non-compartmental methods using the non-compartmental pharmacokinetic analysis program WinNonlin Professional Version 1.5. All calculations were based on actual sampling times. Pharmacokinetic parameters determined included maximum observed plasma concentration ( $C_{max}$ ) and time to reach maximum plasma concentration ( $T_{max}$ ). The apparent terminal elimination rate constant ( $l_z$ ) was derived from the log-linear disposition phase of the concentration-time curve using linear least-squares regression with visual inspection of the data to determine the appropriate number of points to calculate  $l_z$ . The apparent terminal elimination half-life ( $T_{1/2}$ ) was calculated as  $\ln(2)/l_z$ .

Area under the plasma concentration-time curve from time zero to the last quantifiable plasma concentration [ $AUC(0-t)$ ] was determined using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid [Chiou WL., J. Pharmacokinet. Biopharm., 1978, 6, 539-547]. The area under the plasma concentration-time curve extrapolated to infinity [ $AUC(0-\infty)$ ] was calculated as the sum of  $AUC(0-t)$  and  $C(t)/l_z$ , where  $C(t)$  was the predicted concentration from the log-linear regression analysis at the last measurable time point.

The time above the minimum inhibitory plasma concentration ( $T > MIC$ ) was calculated manually by graphical interpolation, where the minimum inhibitory plasma concentrations was defined as 4  $\mu g/mL$  for amoxicillin.

The mean concentration-time profiles for amoxicillin and for clavulanate were derived at each nominal sampling time for each formulation. In cases where a post-dose value was not quantifiable, a value of 1/2 the LLQ (0.050  $\mu g/mL$ ) was assigned to determine the mean value. Where the calculated mean value was less than the LLQ or was based on greater than 50% NQ values, a value of NQ was assigned for that sampling time.

$\log_e$ -transformed  $C_{max}$  and untransformed  $T > MIC$  for each of the formulations were analysed using Analysis of Covariance (ANCOVA) fitting a single term for formulation and fitting the data from the reference formulation as a co-variate. The 95% confidence intervals for the means of each formulation were constructed using the residual variance from the model. For  $C_{max}$ , the confidence interval estimates on the log scale were then back-transformed to obtain the 95% confidence intervals of the geometric mean. These results were displayed graphically.

Assumptions underlying the analyses were assessed by inspection of residual plots. Homogeneity of variance was assessed by plotting the studentised residuals against the predicted values from the model, while normality was assessed using normal probability plots. Particular attention was paid to any outlying values observed with the reference  
5 formulation.

### Study A

The first study compared three modified release dosages of 1750/125 mg (formulations I to III) and a fourth modified release dosages of 1500/125 mg (formulation IV) against an immediate release dosage of 1750/125 mg (formulation V), as follows:

- 10 (a) a dosage of 1750/125 mg amoxicillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg amoxicillin trihydrate/clavulanate and 4% xanthan gum and one immediate release tablet comprising 875 mg amoxicillin trihydrate (formulation I);
- 15 (b) a dosage of 1750/125 mg amoxicillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg crystallised sodium amoxicillin/clavulanate and 4% xanthan gum and one immediate release tablet comprising 875 mg amoxicillin trihydrate (formulation II);
- 20 (c) a dosage of 1750/125 mg amoxicillin/potassium clavulanate, made up of a combination of one modified release tablet comprising 875/125 mg crystallised sodium amoxicillin/clavulanate, citric acid (156 mg) and 2% xanthan gum and one immediate release tablet comprising 875 mg amoxicillin trihydrate (formulation III);
- 25 (d) a dosage of 1500/125 mg amoxicillin/potassium clavulanate (made up of a modified release tablet comprising 500/125 mg crystallised sodium amoxicillin/potassium clavulanate and two immediate release tablet comprising 500 mg amoxicillin trihydrate (Amoxyl, SmithKline Beecham) (formulation IV); and
- 30 (e) a dosage of 1750/125 mg amoxicillin/potassium clavulanate, made up of a combination of one immediate release tablet comprising 875/125 mg amoxicillin trihydrate/clavulanate (Augmentin, SmithKline Beecham) and one immediate release tablet comprising 875 mg amoxicillin trihydrate (Amoxyl, SmithKline Beecham) (formulation V).

## Results

| Formulation | n  | C <sub>max</sub> <sup>1</sup> | T>MIC <sup>1,2</sup> | AUC <sup>1,3</sup> |
|-------------|----|-------------------------------|----------------------|--------------------|
| I           | 8  | 12.75 (4.96)                  | 4.5 (1.8)            | 47.83              |
| II          | 8  | 18.56 (4.72)                  | 4.4 (1.0)            | 57.46              |
| III         | 8  | 13.03 (2.34)                  | 5.73 (2.54)          | 54.93              |
| IV          | 8  | 17.33 (4.66)                  | 4.8 (0.9)            | 56.71              |
| V           | 40 | 20.21 (6.09)                  | 4.2 (0.9)            | 56.33              |

( ) standard deviation

<sup>1</sup> arithmetic mean value

5 <sup>2</sup> T>MIC is the time (h) above an amoxicillin concentration of 4 µg/ml

<sup>3</sup> Area under the curve (0 to 12 h, µg.h/mL)

The pharmacokinetic profile is shown in Figure 4.

### 10 Study B

The second study investigated two different modified release dosages of 2000/125 mg (formulations VI and VII) against an immediate release dosage of 2000/125 mg (formulation VIII), as follows:

- 15 (a) a dosage of 2000/125 mg amoxicillin/potassium clavulanate, made up of two bilayer tablets according to Example 1 (formulation VI);
- (b) a dosage of 2000/125 mg amoxicillin/potassium clavulanate, made up of two bilayer tablets according to Example 2 (formulation VII);
- 20 (c) a dosage of 2000/125 mg amoxicillin/potassium clavulanate, made up of a combination of three tablets each comprising 500 mg amoxicillin (Amoxyl, SmithKline Beecham) and one tablet comprising 500 mg amoxicillin and 125 mg potassium clavulanate (Augmentin, SmithKline Beecham) (formulation VIII).

## Results

| Formulation | N  | C <sub>max</sub> <sup>1</sup> | T>MIC <sup>1,2</sup> | T>MIC <sup>1,3</sup> | AUC <sup>1,4</sup> |
|-------------|----|-------------------------------|----------------------|----------------------|--------------------|
| VI          | 7  | 17.41 (1.93)                  | 6.0 (1.3)            | 4.8 (1.2)            | 74.9               |
| VII         | 8  | 17.46 (6.02)                  | 5.9 (1.3)            | 4.0 (1.3)            | 71.5               |
| VIII        | 12 | 23.75 (5.73)                  | 4.9 (1.1)            | 3.5 (1.0)            | 69.2               |

( ) standard deviation

5 1 arithmetic mean value

2 T>MIC is the time (h) above an amoxicillin concentration of 4 µg/ml

3 T>MIC is the time (h) above an amoxicillin concentration of 8 µg/ml

4 Area under the curve (0 to 12 h, µg.h/mL).

10 Comparison of the AUC values for formulations VI and VII (bilayer tablets) against VIII (immediate release tablets) shows that the absorption of the amoxicillin component has not been compromised by formulating a part of it in a slow release layer. This means that there is no extra, unabsorbed amoxicillin which may otherwise cause problems further down in the GI tract, for instance due to a lack of absorption and destruction of  
15 symbiotic bacteria

It was also found that for formulation VI, there was less inter-subject variability in the amoxicillin plasma concentrations than for formulation VII. These formulations were the same, except that formulation VI also comprised xanthan gum (2%) in the slow  
20 release layer.

The pharmacokinetic profile for amoxicillin plasma concentration is shown in Figure 5 (in which A is formulation VI, B is formulation VII, D is formulation VIII).

25 The pharmacokinetic profile for the clavulanate component was substantially the same for the bilayer tablets and the immediate release tablets, showing that the bioavailability thereof was not compromised by incorporation into the immediate release layer of a bilayer tablet.

### 30 Study C

In a further study, the pharmacokinetic profile of the following dosage regimens was determined:

(a) 2000/125 mg, using two monolith tablets of Example 5 (Formulation IX);

(b) 2000/125 mg, using an 875 mg tablet of Example 7 in combination with an 875 mg tablet of amoxicillin and a 250/125 mg tablet of amoxicillin/clavulanate (Formulation X);

5 (c) 2000/125 mg, using an 875 mg tablet of Example 8 in combination with an 875 mg tablet of amoxicillin and a 250/125 mg tablet of amoxicillin/clavulanate (Formulation XI); and

(d) 2000/125 mg, using an 875 mg tablet of Example 9 in combination with an 875 mg tablet of amoxicillin and a 250/125 mg tablet of amoxicillin/clavulanate (Formulation XII).

10

## Results

| Formulation | N  | C <sub>max</sub> <sup>1</sup> | T>MIC <sup>1,2</sup> | T>MIC <sup>3</sup> | AUC <sup>1,4</sup> |
|-------------|----|-------------------------------|----------------------|--------------------|--------------------|
| IX          | 11 | 20.84 (8.23)                  | 5.95 (1.23)          | 4.8                | 79.9 (26.5)        |
| X           | 11 | 18.73 (5.57)                  | 5.14 (1.28)          | 3.5                | 64.8 (21.1)        |
| XI          | 11 | 18.73 (4.55)                  | 5.47 (1.16)          | 3.5                | 69.2 (18.6)        |
| XII         | 11 | 16.67 (4.04)                  | 6.01 (1.62)          | 3.1                | 65.2 17.4)         |

( ) standard deviation

<sup>1</sup> arithmetic mean value

15 <sup>2</sup> T>MIC is the time (h) above an amoxicillin concentration of 4 µg/ml

<sup>3</sup> T>MIC is the time (h) above an amoxicillin concentration of 8 µg/ml

<sup>4</sup> Area under the curve (0 to 12 h, µg.h/mL).

20 The present invention also extends to formulations which are bioequivalent to the tablets of formulations VI and VII, in terms of both rate and extent of absorption, for instance as defined by the US Food and Drug Administration and discussed in the so-called "Orange Book" (Approved Drug Products with Therapeutic Equivalence Evaluations, US Dept of Health and Human Services, 19th edn, 1999).

## 25 Reference Data

The existing Augmentin 875/125mg tablet has a C<sub>max</sub> value of 11.6±2.8 µg/ml (Physicians Desk Reference, Medical Economics Co, 52 edition, 1998, 2802). The time above MIC was about 40% of the 12 hour dosing interval for an MIC of 2 µg/ml and  
30 about 30% for an MIC of 4 µg/ml (SmithKline Beecham data).